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Paediatric and Adolescent Alveolar Soft Part Sarcoma: A Joint Series From European Cooperative Groups

D. Orbach, MD,[1]* B. Brennan, MD,[2] M. Casanova, MD,[3] C. Bergeron, MD,[4] V. Mosseri, MD,[5] N. Francotte, MD,[6] M. Van Noesel, MD, PhD, MSc,[7] A. Rey, MD,[8] G. Bisogno, MD,[9] G. Pierron, MD,[10] and A. Ferrari, MD[3]

Background. Alveolar soft part sarcomas (ASPS) are generally chemo- and radio-resistant mesenchymal tumours, with no standardized treatment guidelines. We describe the clinical behaviour of paediatric ASPS and compare these features to previously reported adult series. ***Patients and Methods.*** The clinical data of 51 children and adolescents with ASPS, prospectively enrolled in or treated according to seven European Paediatric trials were analysed. ***Results.*** Median age was 13 years [range: 2–21]. Primary sites included mostly limbs (63%). IRS post-surgical staging was: IRS-I (complete resection) 35%, II (microscopic residual disease) 20%, III (gross residual disease) 18% and IV (metastases) 27%. Only 3 of the 18 evaluable patients (17%) obtained a response to conventional chemotherapy. After a median follow-up of 126 months (range: 9–240), 14/18 patients with IRS-I tumour, 10/10 IRS-II, 7/9 IRS-III and 2/14 IRS-IV were alive in remission. Sunitinib treatment achieved two very good partial responses in four patients. Ten-year overall survival (OS) and event free survival (EFS) was $78.0 \pm 7\%$ and $62.8 \pm 7\%$ respectively. Stage IV, size >5 cm and T2 tumours had a poorer outcome, but only IRS staging was an independent prognostic factor. ***Conclusions.*** ASPS is a very rare tumour frequently arising in adolescents and in the extremities, and chemo resistant. Local surgical control is critical. ASPS is a poorly chemo sensitive tumour. For IRS-III/IV tumours, delayed radical local therapies including surgery are essential. Metastatic patients had a poor prognosis but targeted therapies showed promising results. Pediatr Blood Cancer 2013;60:1826–1832. © 2013 Wiley Periodicals, Inc.

Key words: adolescence; Alveolar soft part sarcoma; chemotherapy; childhood; radiotherapy; target therapy

INTRODUCTION

Alveolar Soft Part Sarcoma (ASPS) is a rare, malignant, mesenchymal tumour characterized by an unbalanced recurrent t (X;17)(p11.2;q25) translocation, which leads to a chimeric ASPSCR1-TFE3 transcription factor [1]. ASPS is characterized by uniform, organoid nests of polygonal tumour cells, separated by fibrovascular septa and delicate capillary-sized vascular channels [2]. ASPS can occur at any age [1,3–5], with a peak incidence in the third decade. About one third of ASPS occur in children and adolescents. Paediatric oncologists usually classify ASPS in the heterogeneous group of non-rhabdomyosarcoma soft tissue sarcomas (NRSTS), in which ASPS represents 4.5% of all tumour types [6,7]. In adulthood, ASPS accounts for 0.7% of all soft tissue sarcomas [2,5]. Due to the rarity of this disease, no standardised treatment guidelines have yet been defined. Surgery remains the mainstay of treatment with an R0 resection critical for a good outcome in localized ASPS. However, surgery alone may not be sometime feasible or sufficient, as local recurrence is possible after adequate resection, and metastases (lung or brain) may occur, sometimes years after the initial diagnosis [4]. ASPS is reported to be chemo insensitive, with a complete/partial remission rate of less than 10% with conventional chemotherapy [5]. In a previous paediatric series, only two out of seven evaluable patients reportedly obtained a clinical partial response [3]. Targeted therapies such as multiple tyrosine kinase receptor inhibitors (RTKs) or anti-angiogenic therapy (i.e. sunitinib, cediranib or bevacizumab) have been shown to be effective in adult ASPS [8–11]. Although the extreme rarity of ASPS in children precludes exclusively paediatric studies on this specific histotype, recent data indicate that paediatric cases might be equally sensitive to new targeted therapies [11,12], but further data are needed to confirm this finding.

We therefore retrospectively analysed the clinical data of various ASPS cases prospectively registered and treated in various European paediatric cooperative groups and compared these features to previously reported adult series.

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METHODS

Study Population

The study concerned a series of 51 previously untreated patients with a diagnosis of ASPS: 23 cases were prospectively registered in Italian protocols, 17 cases enrolled in the International Society of Paediatric Oncology Malignant Mesenchymal Tumour group protocols; another 11 French cases were collected from the Institut Curie Genetic Laboratory. All these patients were treated according to the on-going European paediatric protocol at time of diagnosis. Thirteen of these patients have been already included in previous publications [3,10,13]. Inclusion criteria for this study were: (1) study period: 1980–2009; (2) patient's age: 0–21 years; (3) histological diagnosis of ASPS after panel confirmation or presence of ASPSCR1-TFE3 fusion transcript in a non-renal soft tissue tumour [14].

Tumour site was defined as extremities (including the limb girdles, i.e. inguinal region, hip, buttock and shoulder) or axial sites

[1]Department of Paediatric Oncology, Institut Curie, Paris, France; [2]Department of Paediatric Oncology, Royal Manchester Children's Hospital, Manchester, United Kingdom; [3]Paediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumouri, Milano, Italy; [4]Institut d'Hématologie et d'Oncologie Pédiatrie, Lyon, France; [5]Department of Biostatistics, Institut Curie, Paris, France; [6]Department of Paediatrics, CHC-Clin Espérance—rue Saint Nicolas, Montegnée, Belgium; [7]Department of Paediatric Oncology-Hematology, Erasmus MC/Sophia Children's Hospital, Rotterdam, The Netherlands; [8]Department of Biostatistics, Institut Gustave Roussy, Villejuif, France; [9]Paediatric Hematology and Oncology Division, Padova University, Padova, Italy; [10]Somatic Genetic Unit, Institut Curie, Paris, France

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*Correspondence to: Daniel Orbach, Department of Adolescent Paediatric Oncology, Institut Curie, 26 rue d'Ulm, 75231 Paris Cedex 05, France. E-mail: daniel.orbach@curie.net

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(i.e. head and neck, lung and pleura, retroperitoneum, trunk (thoracic and abdominal wall)). Staging in all protocols included lung computed tomography (CT) scan of the lung, bone marrow aspiration and biopsies, and Technetium bone scanning. Tumour stage was defined according to the paediatric pretreatment TNM system (T1 or T2 according to the invasion of contiguous organs, A or B according to tumour diameter $\leq$5 or $>$5 cm, respectively; N0 or N1, and M0 or M1 according to the presence of lymph node or distant metastases) and the Intergroup Rhabdomyosarcoma Study (IRS) post-surgical grouping classification (group I: complete resection, group-II: microscopic residual disease, group-III: gross residual disease, group-IV: metastases at onset) [15]. As centralized pathology review had already been set up in each collaborative group, histological diagnoses were not specifically reviewed for this analysis.

Treatment Modalities

Patients received multi-modal treatments including surgery, radiotherapy and chemotherapy, according to the paediatric treatment protocols in use at the time. The general treatment strategy did not change substantially over time, or between the various protocols. Attempted conservative surgery was the mainstay of treatment: primary excision was planned when it was expected to be complete and non-mutilating, otherwise biopsy was performed. Primary re-excision was recommended prior to any other therapy in the case of suspected microscopic residual tumour, in an attempt to achieve a complete resection. If conservative complete excision was considered unfeasible at the time of diagnosis, surgery was delayed until after chemotherapy to induce tumour shrinkage and improve resectability [7,13].

Radiotherapy was considered for all patients at high risk of local relapse due to either tumour size ($>$5 cm) or incomplete resection [7]. External beam irradiation to the primary tumour was administered with conventional fractionation (1.8–2 Gy/day) for a total dose ranging from 40 to 50 Gy. According to the protocol, the irradiation target volume included the initial tumour plus 2–3 cm margin and the surgical scar.

Chemotherapy was used in selected cases, either in the presence of microscopic or gross residual disease after surgery, according to the various protocols, usually ifosfamide-doxorubicin based regimens [6,13]. Response to chemotherapy in patients with measurable disease was evaluated after three cycles and was based on the radiological detectable reduction in the sum of the products of the perpendicular diameters of all measurable lesions. Response was defined as: complete (CR) = complete disappearance of disease; partial (PR) = tumour reduction $>$50%; minor (MR) = reduction $>$25%. Stable disease or tumour reduction $<$25% was classified as no response, whilst an increase in tumour size or detection of new lesions was considered to be progression.

Statistical Methods

Local control was defined as control of the primary tumour with disappearance of all clinical and radiological signs of disease, or stable residual radiographic images for at least 12 months after completion of treatment. Outcome was defined by overall survival (OS) and event-free survival (EFS). For EFS, events were defined as relapse after CR, failure of tumour local control, progressive of metastatic disease, or death from any cause. In the case of no initial control of tumour the time-point taken into account for the event was the date of the beginning of therapy. Survival curves were computed by the Kaplan–Meier method. The statistical significance of each variable was tested by the log-rank test (univariate analysis). Ten-year survival rates are expressed together with the standard error. Multivariate analysis of 10-year EFS was performed using the Cox proportional hazards regression model.

RESULTS

Patient and Tumour Characteristics

Clinical characteristics of the 51 patients are shown in Table I. Briefly, 69% of cases were over 10 years of age; 57% were female; the primary tumour was located in the extremities in 63% of cases, in the head and neck region in 15% (5 patients had a tongue primary) and in the trunk in 18%. Primary tumour was classified as

TABLE I. Clinical Characteristics and Outcome of 51 Patients With Alveolar Soft Part Sarcoma

	Number of patients	Frequency	Median (ranges)
Gender (male/female)	22/29		
Age (year)	—	—	13 (2–21)
Initial site			
Limbs	32 pts	63%	
Head and neck	8 pts	15%	
Abdomen	6 pts	12%	
Thorax	3 pts	6%	
Orbit	2 pts	4%	
TNM classification			
T I/T II[a]	35/13 pts	73%/27%	
A/B	27/24 pts	53%/47%	
Nodal status: N+	3 pts	6%	
IRS group			
IRS I (complete resection)	18 pts	35%	
IRS II (microscopical residue)	10 pts	20%	
IRS III (macroscopical residue)	9 pts	18%	
IRS IV (metastasis)	14 pts	27%	

Pts, patients. [a]Missing data for 3 pts.

T1aA in 54% of cases, T1B in 21%, T2A in 2% and T2B in 25%. Regional lymph node involvement was reported in only three cases (6%).

Subgroup Analysis

IRS-I group. This group represents 18 patients with initial complete resection. All but one case had a T1 tumour (missing data in 2 patients) and all but four cases had tumours less than 5 cm at diagnosis. Adjuvant chemotherapy was administered to seven patients, and in two patients adjuvant radiotherapy at a dose of 55.8 or 50 Gy in addition to chemotherapy in one patient. At the time of analysis, 14 patients were alive in first remission, 17–240 months from diagnosis (median: 131 months). Four patients had a metastatic relapse (three in the lung only, one in lung and brain) at 18–110 months after diagnosis. One of these patients had received adjuvant chemotherapy as a front-line treatment. One of the relapsed patients died of disease; one developed a secondary acute leukaemia 2 years after the second remission of ASPS and is alive 10 years from the end of therapy; the third is currently receiving sunitinib therapy after failure of various chemotherapy regimens, and the last patient was alive in remission 18 months after relapse.

IRS-II group. Microscopic residual disease after first surgery was present in 10 patients. All but one of the patients in this subgroup had a T1A tumour. Seven patients received adjuvant chemotherapy, in combination with radiotherapy (45–53 Gy) for five patients, and one patient received exclusive adjuvant radiotherapy at 54 Gy. All patients were alive in first remission at the time of the report (follow-up: 11–199 months, median: 150 months).

IRS-III group. For nine patients, IRS grouping was classified as III for gross residual disease after biopsy (eight cases) or initial incomplete surgery (one case). In 6 cases, the tumour was larger than 5 cm. All nine patients received chemotherapy, five underwent delayed surgery (complete in three cases (i.e. margins negative) and unknown in two cases), with radiotherapy for six patients (45–60 Gy, median: 55 Gy). In this subgroup, 7/9 patients were in first remission at the time of the report, 59–155 months after diagnosis (median: 110 months). Two patients relapsed, one locally and one locally with lung metastases, after 20 and 2 months, respectively. First-line local treatment in these two patients was exclusive radiotherapy. Both patients died of disease. Only one patient, treated with definitive radiotherapy, had a durable local tumour control.

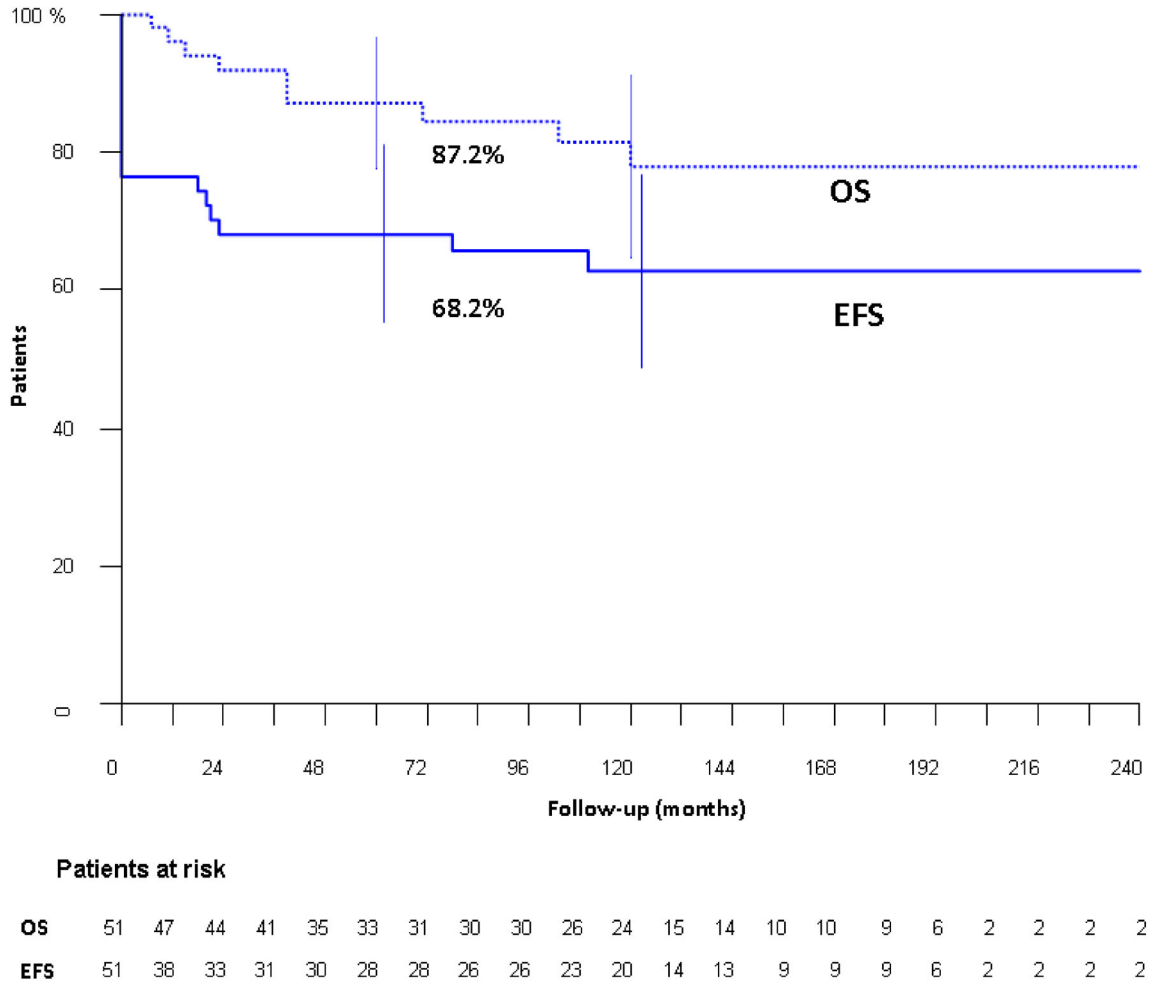

Fig. 1. Overall (OS) and event-free survival (EFS) of the overall population.

IRS-IV group. Distant metastases were present at diagnosis in 14 cases. All but one case had a tumour larger than 5 cm. In 13 patients (93%), the lung was the site of metastases (associated with bone metastases in two cases and liver metastases in one case); one patient had isolated bone metastasis. Three patients also had regional lymph node involvement. One patient refused treatment and was lost to follow-up with progression. All other cases received various chemotherapy regimens; nine received adjuvant radiotherapy (36–50.4 Gy). Eleven of the 13 evaluable patients experienced tumour progression or relapse, two locally, three locally plus metastases, six at metastatic sites only. Sunitinib was administered on compassionate grounds to four patients with a very good partial response of the lung metastases in two patients, stable disease in one patient still on therapy after 6 months and 1 failure due to patient refusal after severe prolonged cutaneous adverse events despite tumour stabilization after 12 months of therapy. Sunitinib therapy was not strictly uniform. All four patients are alive at the end of follow-up with stable residual pulmonary images. Six patients out of the 14 died of disease. Overall, only two patients were in continuous remission at the time of the report, 121 and 185 months after diagnosis, respectively. These two patients received various types of chemotherapy and a complete resection of all pulmonary metastasis after bilateral thoracotomies. Another patient was in second remission with surgery for lung metastases and various chemotherapy regimens (six drugs regimen, 5-fluorouracil-cisplatinum, Interleukine 2) after pulmonary progression. Four other patients were alive on treatment after various systemic salvage therapies.

Overall Response Rate to Systemic Therapy

In summary, 3 of the 18 patients with evaluable IRS-stage III–IV ASPS obtained a response to initial conventional chemotherapy (17%) with one complete remission and two partial responses with VACA/VAIA regimens. Twelve patients had a stable disease and three patients a progressive disease. Response to sunitinib, given after tumour relapse or progression, consisted of two very good partial responses and two cases of stable disease.

Overall Outcome and Prognostic Variables

After a median follow-up of 126 months (range: 9–240 months), 33 patients were alive in first remission, 3 in second remission and 6 were alive with disease. Nine patients died of disease. Among the 12 patients with progressive disease in which data are available, 4 developed brain metastasis during progression as well as lung metastasis. Data was not specified for 5 patients. Only 3 of the 10 patients alive after relapse were disease-free after a long follow up. In summary, 90% of patients with localized tumour had a grossly resected tumour defined by IRS group I/II and group III with complete delayed resection. Five- and 10-year EFS were $68.2 \pm 7\%$ and $62.8 \pm 7\%$; 5- and 10-year OS were $87.2 \pm 5\%$ and $78.0 \pm 7\%$, respectively (Fig. 1). Table II describes the statistical analysis. IRS grouping, size and TNM classification were important prognostic risk factors for EFS and OS. Age did not appear to be a prognostic factor. Similar results were observed for 10-year survival rates (data not shown). Initial tumour extension was the only significant prognostic factor for EFS in the multivariable model (IRS group I–II–III vs. IV, Relative risk: 12.50 [4.6–34.3]). Valid statistical comparison of OS could not be performed due to the small numbers of events.

DISCUSSION

This series of paediatric ASPS cases recruited by various paediatric European cooperative groups can be considered to be the most extensive clinical description of this tumour in children and adolescents. The primary objective of this study was to describe the

TABLE II. Survivals According to Risk Factors

	Univariate analysis				Multivariate analysis
Risk factors	EFS		OS		EFS
IRS groups		$P < 0.0001$		$P < 0.002$	$P < 0.00001$
IRS-I (18 pts)	$72.8 \pm 12\%$		$91.7 \pm 8\%$		
IRS-II (10 pts)	100%		100%		
IRS-III (9 pts)	$77.8 \pm 14\%$		$66.7 \pm 21\%$		
IRS-IV (14 pts)	$14.3 \pm 9\%$		$44.8 \pm 17\%$		
Age		$P > 0.30$		$P > 0.29$	—
<12 years (25 pts)	$71.6 \pm 9\%$		$83.5 \pm 9\%$		
>13 years (26 pts)	$54.8 \pm 10\%$		$72.8 \pm 10\%$		
Gender		$P > 0.89$		$P > 0.60$	—
Female (29 pts)	$65.2 \pm 9\%$		$78.0 \pm 8\%$		
Male (22 pts)	$58.3 \pm 12\%$		$76.1 \pm 12\%$		
Tumour site		$P > 0.69$		$P = 0.90$	—
Limbs (32 pts)	$67.7 \pm 11\%$		$82.1 \pm 9\%$		
Axial (19 pts)	$59.8 \pm 9\%$		$75.5 \pm 9\%$		
Tumour size		$P < 0.0001$		$P < 0.0001$	$P > 0.10$
<5 cm (27 pts)	$87.3 \pm 7\%$		100%		
>5 cm (24 pts)	$34.8 \pm 10\%$		$44.8 \pm 14\%$		
TNM		$P < 0.0065$		$P < 0.0001$	$P > 0.10$
T1 (35 pts)	$75.1 \pm 8\%$		$91.3 \pm 6\%$		
T2 (13 pts)	$38.5 \pm 13\%$		$44.9 \pm 14\%$		

Pts, patients.

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TABLE III. Main Studies Published on Alveolar Soft Part Sarcomas

	Number of patients	Median age year [ranges]	Limbs primary	Metastatic	5-year EFS	5-year OS	Adverse prognostic factors	Notes
Paediatric series								
Current series, Europe, 2012	51	13 [2–21]	63%	27%	63.8 ± 7%	78 ± 6.7%	Metastasis	—
Kayton M. USA, 2006	20	16.5 [6–24]	50%	37%	22%	83%	Size >5 cm. Not age	Relatively good prognosis despite metastasis in 70% of cases
Casanova M. Italy, 2000	19	12 [4–18]	53%	21%	—	80%	Metastasis, size >5 cm. Not age, gender, site and type of treatment	Importance of surgery
Pappo. USA, 1996	11	9.6 [2.8–16]	36%	18%	—	85%	—	Importance of tumour resectability
Adult series								
Daigeler A. Germany, 2008	11	32 [19–49]	75%	0%	—	58%	—	
Lazar A. USA, 2007	33	28	—	—	—	74%	—	Analysis of angiogenesis promoting gene patterns: ASPS angiogenic signature is specific
Jong R. Canada, 1998	9	46 [18–70]	86%	33%	—	—	—	Clinicopathological analysis: some unusual histopathological features are possible
Combined age series								
Ogura K. Japan, 2012	26	27 [2–46]	69%	62%		64%	Size, AJCC stage	Age ±18 year is not a prognostic factor
Rekhi B. India, 2012	47	24 [2–54]	67%	48%	—	100%	—	Short FU of only 22 pts. TFE3 is a useful marker for diagnosis
Williams A. UK and Sweden, 2011	18	23 [3–46]	89%	39%	—	—	—	ASPL/TFE3 fusion transcripts are powerful tools for diagnosis
Jun H. Korea, 2010	12	29 [12–57]	50%	50%	—	53%	Metastasis	The high level of expression of MET in ASPL-TFE3 support potential role of targeted agents
Pennacchioli E. Italy, 2010	33	39 [7–62]	79%	36%	—	68.7%	Quality of surgery, size >5 cm	Importance of tumour resectability. Distant metastases fairly common, typical indolent course
Pang L. China, 2008	16	26[3–58]	50%	12.5%	—	—	—	
Reichardt P. Germany, 2003	8	29[15–43]	88%	100%	—	—	—	High incidence of brain metastases. ASPS patients should not be treated with CT except in controlled clinical trials
Ogose A. Japan, 2003	57	25 [7–75]	84%	64%	—	56%	Metastasis, tumour size and bone involvement at primary. Not age, gender, site and type of chemotherapy	No multivariate analysis performed. No advantage could be demonstrated for CT with high-dose ifosfamide or cisplatin
Van Ruth S. the Netherlands, 2002	15	27 [1–52]	73%	33%	—	38%	—	Importance of tumour resectability. Poor prognosis in the presence of metastasis
Portera C. USA, 2001	74	26 [3–68]	60%	65%	L: 71%	M: 20% L: 88%	Metastasis	Relatively indolent clinical course. Routine intracranial imaging should be used
Lieberman P. USA, 1989	102	27 [5–56]	74%	23%	—	62%	Metastasis, tumour size, adults. Not gender; nor laterality	Importance of tumour resectability. Long survival may be observed, even with metastases
Evans H. USA, 1985	14	23 [5–59]	50%	21%	NA	50%	Metastasis, tumour size	

CT, chemotherapy; EFS, event-free survival; OS, overall survival; L, localized; M, metastatic; FU, follow-up.

clinical findings and behaviour of this rare malignancy. Furthermore this study was set up to analyse therapeutic considerations according to initial tumour staging and resectability. It confirmed the previous findings of chemo insensitivity in ASPS with only 17% of the evaluable patients responding to chemotherapy, other studies reporting an overall response rate of between 0% and 30% [3–5,16–19]. The role of adjuvant chemotherapy is unclear on the basis of our results. One out of 14 patients with grossly resected tumour at diagnosis (IRS-I or II) treated with chemotherapy had a metastatic relapse versus 3 out of 14 who did not receive any adjuvant chemotherapy. Other drugs in ASPS may have an anti-angiogenesis effect, such as bevacizumab [9], sunitinib [10–12] or interferon alpha-2b [20]. Phase II trials with cediranib and a c-Met inhibitor (ARQ-197) have recently confirmed the efficacy of these drugs [8,21]. Data on efficacy of anti-angiogenesis drugs in ASPS are limited in children and most of them are scared and coming from retrospective study. Our limited experience would suggest that sunitinib may constitute a potential treatment option for patients with unresectable or metastatic disease [10]. Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases, some of which are involved in tumour growth, angiogenesis and metastatic progression of cancer. The use of sunitinib has a rational basis, in that MET autophosphorylation, due to the ASPSCR1-TFE3 fusion protein, activates cell signalling pathways governing angiogenesis, cell division and growth, and cell survival [22,23]. Moreover, sunitinib has also been shown to be effective in the Xp11 renal cell carcinoma (RCC), which is known to sometimes share the same transcript, with objective responses and prolonged progression-free survival. In RCC either, translocation involves the transcription factor E3 (TFE3) gene located on Xp11.2. The TFE3 protein encoded by this gene interacts with same transcription cell regulator agents. In this latter tumour, the most common translocations involve an alveolar soft part sarcoma locus (ASPL)-TFE3 or renal cell carcinoma (RCC) papillary 1 gene (PRCC)-TFE3 fusion [24].

Although this study analysed a large series of paediatric ASPS, each subset comprised of only a few cases and the small sample size therefore prevents any valid conclusions concerning treatment. Surgery has been shown to play a critical role in achieving local control. The fairly satisfactory survival rates observed in our cohort of patients with localized tumours is related to the high resectability rate, possibly due to their initial presentation with a relatively small tumour (53% of cases <5 cm), and the majority non-invasive (73% T1). In contrast, our analysis does not provide any arguments in favour of the systematic use of radiotherapy in patients with IRS group-II or -III tumours. In IRS II tumours no local relapse occurred even though 72% of patients did not received any adjuvant radiotherapy.

Comparison of this paediatric series with published series of adult ASPS, as reported in Table III, did not demonstrate any major differences compared to ASPS in children [1,3–5,16–19,25–34], with identical female sex predominating in both populations. Clinical findings were also similar in terms of distribution of tumour sites, chemo insensitivity, a high rate of resectability and the development delayed pulmonary or cerebral metastasis. However, adult patients present with a higher percentage of metastases at diagnosis and larger tumours, two variables that may be associated with a poorer overall prognosis. The present series also suggests a relationship between large tumour size and the presence of metastases, as all patients with metastases bar one had a tumour larger than 5 cm. Tumour size larger than 5 cm was also correlated to a worse prognosis in other studies in children or adults but without multivariate analysis [3–4,30–31].

The study confirms the tendency of ASPS to metastasize, mainly to the lung, with 27% of patients presenting with distant metastases, compared to the 3% reported in large series of various adult-type NRSTS [7]. In patients with localized disease, however, tumours were often confined to the tissue/organ of origin, with no local invasion and with small tumours. Due to the absence of bone marrow spreading in this tumour, we do not recommend bone marrow analysing for initial staging.

The relatively large difference between EFS and OS is probably due to slow disease progression rather than the ability to salvage relapsed patients, as only 3 of the 10 patients alive after relapse were disease-free. It is notable that some metastatic relapses occurred more than 5-year after diagnosis requiring long term follow-up of all these patients.

Disappointingly, the rarity of this tumour does not allow us to plan future therapeutic trials. In the current NRSTS protocol of the European paediatric Soft tissue sarcoma Study Group (EpSSG), ASPS patients are now included in the large heterogeneous group of adult-type NRSTS, together with other histotypes, managed by surgery, radiotherapy and adjuvant chemotherapy according to the already known risk factors (initial extension, tumour size and site and histological grading) [35]. Due to their chemo insensitivity, new guidelines should be tailored to stress the role of local therapies, in particular surgery of the primary tumour and also for distant metastases either at first presentation or after relapse. Novel targeted therapies, in particular sunitinib, would appear to be a potentially effective treatment option. However, due to its toxicity profile and the lack of knowledge of its long term use, especially in children with this indolent sarcoma, we recommend its use should be restricted to cases of inoperable progressive disease or relapsed tumours in prospective experimental study [36]. Nevertheless, the weaknesses of data in children available until now do not allow us to treat children with this new drug out of a prospective experimental controlled study.

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